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OUTCOME AFTER STEROID WITHDRAWAL IN PEDIATRIC RENAL TRANSPLANT PATIENTS RECEIVING TACROLIMUS-BASED IMMUNOSUPPRESSION[1]

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Background. **Corticosteroids have always been an integral part of immunosuppressive regimens in renal transplantation. The primary goal of this analysis was to assess the safety of steroid withdrawal in our pediatric renal transplant recipients receiving tacrolimus-based immunosuppression.**

Methods. **Between December 1989 and December 1996, 82 renal transplantations were performed in pediatric patients receiving tacrolimus-based immunosuppression. Two of these patients lost their grafts within 3 weeks of transplantation (and were still on steroids at the time of graft loss), and were excluded from further analysis. Seventy-four patients (92.5%) were taken off prednisone a median of 5.7 months after transplantation. Of these 74, 56 (70%) remained off prednisone (OFF), and 18 (22.5%) were restarted on prednisone a median of 14.8 months after discontinuing steroids (OFF → ON). 6(7.5%) were never taken off prednisone (ON). The mean follow-up was 59±23 months.**

Results. **The 1-, 3-, and 5-year actuarial patient survival rates in the OFF group were 100%, 98%, and 96%, respectively; in the OFF → ON group, they were 100%, 100%, and 100%, and in the ON group, they were 100%, 83%, and 83%. The 1-, 3-, and 5- year actuarial graft survival rates in the OFF group were 100%, 95%, and 82%, respectively; in the OFF → ON group, they were 100%, 89%, and 83%; and in the ON group, they were 100%, 50%, and 33%. Two of the six graft losses in the OFF group, three out of four in the OFF → ON Group, and two out of five in the ON group, were to chronic rejection. A time-dependent Cox regression analysis showed that the hazard for graft failure for those who came and stayed off prednisone was 0.178 relative to those who were never withdrawn from prednisone (P=0.005). Patients who were 10 years of age or younger were withdrawn from prednisone earlier (median: 5 months) than those older than 10 years (median: 7.3 months, P=0.02). In addition, patients who never had acute rejection were withdrawn from steroids earlier (median: 5 months) than those who had one or more episodes of acute rejection (median: 7.6 months, P=0.001). There was no effect of donor age, race, sex, recipient race, sex, cadaveric versus living donor, 48-hr graft function, panel reactive antibody, and total HLA mismatches or matches on the likelihood of being weaned off steroids. Serum creatinine at most recent follow-up in the OFF group was 1.2±0.5 mg/dl; in the OFF → ON group, it was 1.8±0.9 mg/dl, and in the ON group it was 2.0 mg/dl (P<0.003). The incidence of rejection in the OFF, OFF → ON, and ON groups was 39%, 77%, and 100%, respectively (P<0.05).**

Conclusion. **These data suggest that steroid with-**

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drawal in pediatric renal transplant patients receiving tacrolimus-based immunosuppression is associated with reasonable short- and medium-term patient and graft survival, and acceptable renal function. Patients who discontinue and then resume steroids had patient and graft survival rates comparable with those in patients who discontinue and stay off steroids, but had a higher serum creatinine and a higher incidence of rejection.

In spite of the well-established side effects associated with their use (*1*), corticosteroids have remained a part of long-term immunosuppression after renal transplantation. With the introduction of tacrolimus, however, steroid withdrawal has been possible in some 70% of successfully transplanted adults and children (*2–9*). In the latter group, significant catch-up growth has been achieved, particularly in preadolescent children (*5*, *6*). An important question, however, concerns the outcome after steroid withdrawal in pediatric patients on tacrolimus. Although this question has been studied in adults (*4*, *7–9*), it has not been investigated in detail in children. We looked at our pediatric renal transplant patients receiving tacrolimus-based immunosuppression and examined the short- and medium-term outcomes after steroid withdrawal.

PATIENTS AND METHODS

Between December 14, 1989, and December 31, 1996, 82 renal transplantations under tacrolimus-based immunosuppression were performed in 81 pediatric patients at the Children's Hospital of Pittsburgh (Table 1). Two grafts were lost within 3 weeks of transplantation and were excluded from further analysis (the recipients were still on steroids at the time of graft loss). The mean recipient age was 10.5±5.1 years (range: 0.7–17.9). Sixty-four (80%) were undergoing their first transplant, and 16 (20%) were undergoing their second (n=10), third (n=5), or fourth (n=1) transplants. Five (6%) had panel-reactive antibody (PRA) levels of 40% or higher, and all of them were undergoing repeat transplantation. There were 68 (85%) Caucasian, 7 (9%) African-American, and 5 (6%) Asian recipients. The causes of end-stage renal disease are listed in Table 2.

The mean donor age was 27.9±14.5 years (range: 0.7–50). Forty-six (58%) kidneys were from cadaveric donors. The mean cold ischemia time was 27.5±8.8 hr (range: 9.3–45.2). There were 34 (42%) living donors. The mean number of HLA matches and mismatches was 2.9±1.3 and 3.0±1.3, respectively. There were four (5%) 0-antigen mismatch cases and one (1%) HLA-identical sibling donor case.

TABLE 1. Recipient/donor demographics

n	80	
Recipient age (yr)	10.5±5.1 (range: 0.7–17.9)	
First transplant	64	(80%)
Repeat transplants	16	(20%)
Second transplant	10	(13%)
Third transplant	5	(6%)
Fourth transplant	1	(1%)
PRA≥40%	5	(6%)
PRA<40%	75	(94%)
Donor age (yr)	27.9±14.5 (range: 0.7–50)	
Living donor	34	(42%)
Cadaveric donor	46	(58%)
Cold ischemia time (hr)	27.5±8.8 (range: 9.3–45.2)	
HLA		
Match	2.9±1.3	
Mismatch	3.0±1.3	
0-Ag mismatch	4	(5%)
HLA-identical LRD	1	(1%)

TABLE 2. Causes of end-stage renal disease

Obstructive uropathy	14 (17%)
Congenital dysplasia	12 (15%)
Membranoproliferative glomerulonephritis	8 (10%)
Focal segmental glomerulosclerosis	7 (9%)
Polycystic kidney disease	4 (5%)
Hemolytic-uremic syndrome	3 (4%)
Prune belly syndrome	3 (4%)
Congenital hypoplasia	3 (4%)
Ureteral reflux	3 (4%)
Chronic glomerulonephritis	2 (2%)
Interstitial nephritis	2 (2%)
Pyelonephritis	2 (2%)
Alport's syndrome	2 (2%)
Cystinosis	2 (2%)
Hereditary nephritis	2 (2%)
Undetermined	11 (14%)

Immunosuppression was with tacrolimus and steroids as previously described (*5*, *6*). Induction antilymphocyte antibody was not used. Eighteen patients (22%) received azathioprine. Mycophenolate mofetil was not used as an initial immunosuppressive agent. The idealized timetable for steroid withdrawal is shown in Table 3. Although there were no formal a priori inclusion or exclusion criteria for steroid withdrawal, patients with multiple rejection episodes were unlikely to be candidates for complete withdrawal. Steroids were tapered and discontinued in patients who maintained stable allograft function as the steroid dosage was gradually decreased. Steroids were restarted in recipients who experienced a rising serum creatinine with biopsy-proven acute rejection. Allograft failure was defined by return to dialysis, repeat transplantation, or death.

Patient survival was calculated from the date of kidney transplantation until death, and graft survival was calculated from the date of kidney transplantation until graft failure or patient death. Survival curves were generated using the Kaplan-Meier (product limit) method and were compared using the log-rank test. Values are presented as mean±SD. A time-dependent Cox regression analysis for hazard assumption was done to compare graft survival in recipients who came off steroids versus those who never came off. A Cox time-dependent covariate $z(t)$ was modeled, so that $z(t) = 1$ if the patient was weaned off at least once, and $z(t)=0$ if the patient was not weaned off by time t.

A multivariate multiple logistic regression analysis was performed to compare the effect of recipient sex, recipient race, delayed graft function, recipient PRA, total HLA matches, total HLA mismatches, donor age, and donor type (cadaveric vs. living related) on steroid withdrawal. The means between groups were compared by

TABLE 3. Steroid dosing: idealized tapering schedule

Time	Dose (mg/kg/day)
Intraoperative	15–25
Postoperative day 1–6	3–10 to 0.3–1
Weeks 2–3	0.25–0.75
Weeks 4–5	0.2 to 0.5–0.6
Weeks 6–7	0.17–0.2 to 0.4–0.5
2 mo	0.17 to 0.25–0.3
2.5 mo	0.15 to 0.13–0.2
3 mo	0.13–0.1
3.5 mo	0.13–0.05
4 mo	0.08–0
5 mo	0.05–0
6 mo	0

one-way analysis of variance. Catagorical data were analyzed by Pearson's chi-square method. *P*-values less than 0.05 were considered statistically significant.

Until June 1994, when tacrolimus was approved by the United States Food and Drug Administration, all transplants were performed under a protocol approved by the Human Rights Committee of the Children's Hospital of Pittsburgh.

RESULTS

The mean follow-up was 59±23 months (range: 11–103). Seventy-four (92.5%) patients were withdrawn from steroids at a median of 5.7 months after transplantation. Fifty-six (70%) remained off steroids, and 18 (22.5%) resumed steroids at median of 14.8 months after steroid withdrawal (of these 18, 7 [39%] were eventually tapered off steroids again). Six (7.5%) patients never came off steroids (Tables 4 and 5). The overall 1-, 3-, and 5-year actuarial patient and graft survival rates were 100%, 97%, and 96%, and 100%, 90%, and 79%, respectively (Fig. 1). The 1-, 3-, and 5-year actuarial patient and graft survival rates for those who came and stayed off steroids (OFF) was 100%, 98%, and 96%, and 100%, 95%, and 82%, respectively (Figs. 2 and 3). Those who came off and later resumed steroids (OFF → ON) had a 1-, 3-, and 5-year actuarial patient survival of 100%, and a 1-, 3-, and 5-year actuarial graft survival of 100%, 89%, and 83% (Figs. 2 and 3). In those who never came off steroids (ON), the 1-, 3-, and 5-year actuarial patient survival was 100%, 83%, and 83%, and the 1-, 3-, and 5-year actuarial graft survival was 100%, 50%, and 33% (Table 4, parts B and C, Figures 2 and 3). Three patients died, 1.3–3.2 years after transplantation. Two were off steroids; one died of pancreatitis, and one died on dialysis, 1.3 and 3.2 years after transplantation (the patient on dialysis had lost her kidney to noncompliance 1.7 years after transplantation). One patient who was on steroids died of fungal sepsis 1.3 years after transplantation. Fifteen patients lost their allografts 1.2–6.6 years after transplantation, to rejection (n=7), recurrent disease (n=5), pancreatitis (n=1), fungal sepsis (n=1), and noncompliance (n=1). In the OFF group, six grafts were lost: two to rejection, two to recurrent disease, one to noncompliance, and one to pancreatitis. In the OFF → ON group, four grafts were lost: three to rejection, and one to recurrent disease. In the ON group, five grafts were lost: two to rejection, two to recurrent disease, and one to fungal sepsis.

There was a higher percentage of patients undergoing repeat transplantation in the ON group (n=5; 83%) compared to OFF group (n=7; 12%), and OFF → ON group (n=4; 22%) (*P*=0.001). The mean PRA was 34.5±38 for the ON group, 5.6±15 (*P*=0.001) for the OFF group, and 4.2±10 for the OFF → ON group (*P*=0.002). A total of 39% of patients in the OFF group had experienced acute rejection before steroid withdrawal. In the OFF → ON group, the incidence of acute rejection was 77% before steroid withdrawal, and 100% after steroid withdrawal. In the ON group, rejection was seen in

TABLE 4. Demographics of steroid withdrawal

	OFF	OFF → ON	ON
n	56 (70%)	18 (22.5%)	6 (7.5%)
Recipient race			
Caucasian	84%	89%	83%
Other	16%	11%	17%
Mean recipient age (yr)	10.3±5.6	10.1±3.9	13.3±3.8
Recipient sex			
Female	29%	39%	67%
Male	71%	61%	33%
Delayed graft function			
Yes	4%	0%	17%
No	96%	100%	83%
Mean recipient PRA	5.7±15.3	4.2±10.6	34.5±38.6[a]
Total HLA matches	3.0±1.3	2.3±1.2	3.0±1.3
Total HLA mismatches	2.8±1.4	3.5±1.2	2.8±1.3
Mean donor age (yr)	27.3±15.2	25.9±13.2	39.3±5.8
Donor type			
Cadaveric	54%	67%	67%
Living related	46%	33%	33%

[a] *P*=0.0001.

TABLE 5. Time to steroid withdrawal and episodes of acute rejection[a]

	OFF	OFF → ON	ON
Time to steroid withdrawal (mo) (mean±SD)	7±4	9±6.5*	
Time to restart steroids after withdrawal (mo) (mean±SD)		18 ±16	
Rejections			
Before withdrawal (%)	39%	77%	100%**
After withdrawal (%)		100%	

[a] *, *P*=NS; **, *P*<0.05.

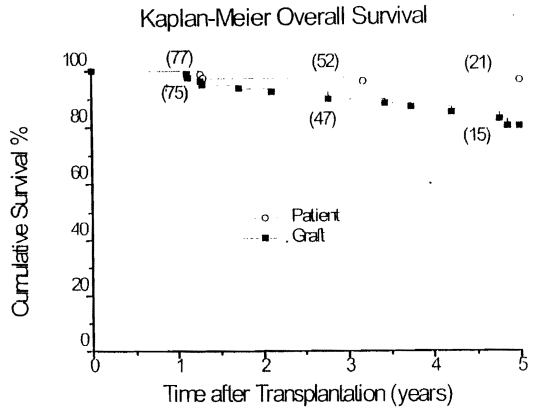

FIGURE 1. Overall actuarial patient and graft survival.

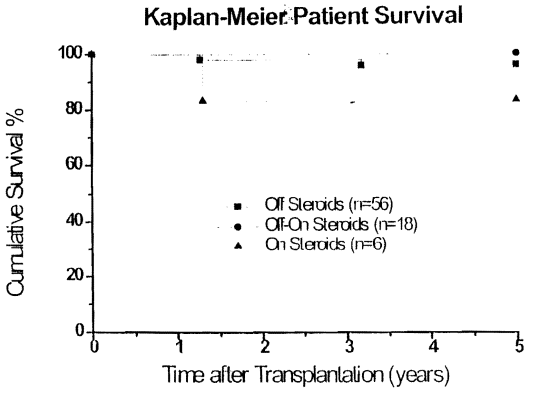

FIGURE 2. Actuarial 1-, 3-, and 5-year patient survival in those off steroids, those off and then back on steroids, and those never off steroids.

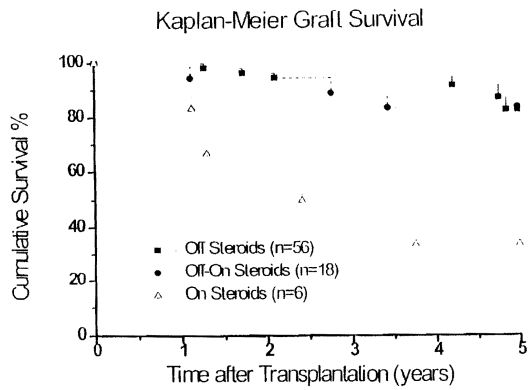

FIGURE 3. Actuarial 1-, 3-, and 5-year graft survival in those off steroids, those off and then back on steroids, and those never off steroids.

100% of patients ($P<0.05$) (Table 5). In recipients with functioning allografts, the mean serum creatinine at most recent follow-up in the OFF group was 1.2±0.5 mg/dl, 1.8±0.9 mg/dl in the OFF → ON group, and 2.0 mg/dl in the one patient with a functioning kidney in the ON group ($P=0.003$). The mean tacrolimus level was 6.3±2.3 ng/ml in the OFF group, 6.5±2.5 ng/ml in the OFF → ON group, and 13.3 ng/ml in the ON group. At most recent follow-up in recipients with functioning allografts, 77% of the patients in the OFF group were off antihypertensive medications, compared with 44% in the OFF → ON group, and 0% in the ON group (Table 6; $P=0.05$). There were no statistically significant differences in the hematocrit, white blood cells, platelets, cholesterol and triglyceride levels, and systolic and diastolic blood pressures among the three groups (Table 6).

In the multivariate analysis, patients who were 10 years of age or younger were withdrawn from prednisone earlier (median: 5 months) than those older than 10 years of age (median: 7.3 months, $P=0.02$). By 2 years after transplantation, 95% of patients 10 years old or younger were weaned off steroids, whereas 90% of patients older than 10 were weaned off steroids. If the patients were not weaned off steroids within the first 2 years, they were unlikely to be weaned off steroids at all. In addition, patients who never had acute rejection were withdrawn from steroids earlier (median: 5 months) than those who had one or more episodes of acute rejection (median: 7.6 months, $P=0.001$). By 2 years after transplantation, 100% of those without an episode of rejection were weaned off steroids, whereas 85% of those with at least one episode of rejection were weaned off steroids. Finally, there were no significant effect of donor age, race, sex, recipient race, sex, cadaveric vs. living related donor, 48-hr graft function, panel reactive antibodies, degree of HLA matching or mismatching, or immunosuppressive regiment (FK+steroids vs. FK+azathioprine+steroids) on the probability of being weaned off steroids.

TABLE 6. Evaluation at most recent follow-up[a]

	OFF	OFF → ON	ON	*P*-value
Creatinine (mg/dl)	1.2±0.5	1.8±0.9	2	0.003
Hematocrit (%)	37.9±3.6	34.7±4.4	25.3	NS
WBC (1×10^3/ml)	6.3±2.1	6.7±1.9	6.5	NS
Platelets (1×10^3/ml)	203±56	241±57	175	NS
Glucose (mg/dl)	92±23	97±23	87	NS
Cholesterol (mg/dl)	160±28	157±18	130	NS
Triglycerides (mg/dl)	120±74	128±58	133	NS
Systolic BP (mmHg)	112±16	125±21	140	NS
Diastolic BP (mmHg)	73±11	80±15	80	NS
Off antihypertensives	77%	44%	0%	0.003
Tacrolimus level (ng/ml)	6.4±2.4	6.6±2.6	13.3	NS

[a] BP, blood pressure; WBC, white blood cells.

DISCUSSION

Corticosteroids have essentially always been an integral part of immunosuppressive regimens in renal transplantation. In order to minimize their well-described side effects, there have been a number of attempts to reduce the dosage of corticosteroids, particularly after the advent of cyclosporine, when further reduction in the maintenance dosage was possible. Several trials have been undertaken to evaluate the outcome of corticosteroid withdrawal in patients receiving cyclosporine-based immunosuppression, with, in the end, not completely satisfactory results and an unacceptably high incidence of late rejection (*9–19*). Most renal transplant patients still receive maintenance corticosteroids chronically.

The primary goal of this analysis was to assess the safety of steroid withdrawal in our pediatric renal transplant recipients receiving tacrolimus-based immunosuppression. Medium-term outcomes suggest that steroid withdrawal was associated with acceptable patient and graft survival and stable renal function. Long-term steroid withdrawal was possible in 70% of patients, with 5-year actuarial patient and graft survival rates of 96% and 82%, an incidence of rejection of 39%, and a mean serum creatinine level of 1.2±0.5 mg/dl. In the 22.5% of patients in whom steroids were withdrawn and then resumed (39% of whom eventually came back off steroids), the 5-year actuarial patient and graft survival rates were 100% and 83%, the incidence of rejection was 77%, and the serum creatinine level was 1.8±0.9 mg/dl. In the small group of patients (7.5%) who never came off steroids, the 5-year actuarial patient and graft survival rates were 83% and 33%, the incidence of rejection was 100%, and the serum creatinine level was 2.0 mg/dl in the remaining patient with a functioning renal allograft. In this latter group, the percentage of patients undergoing repeat transplantation was higher (83%; $P=0.001$), as was the mean PRA (34.5%±38.5%; $P=0.001$), than those in the OFF and OFF → ON groups.

It should be emphasized that patients were not randomly assigned to steroid withdrawal, and patients who never came off steroids had a number of risk factors, including repeat transplantation, sensitization, and acute rejection. The main questions for us concerned the safety of steroid withdrawal and, perhaps more importantly, the outcomes in patients who were withdrawn from and then resumed steroids. Five-year patient and graft survival rates were essentially identical in the OFF and the OFF → ON groups, but the incidence of rejection and the mean serum creatinine were higher in the OFF → ON group, and these findings are of concern with regard to longer-term follow-up. We have previously reported on the benefits of steroid withdrawal in children, including significant catch-up growth, a low incidence of hypertension, and normal cholesterol levels (*5, 6*). Unfortunately, there are no useful markers to identify patients who can be safely withdrawn from steroids.

To summarize, long-term steroid withdrawal in pediatric

renal transplant patients receiving tacrolimus-based immunosuppression was associated with reasonable long-term patient and graft survival and renal function. Patients who discontinued and then resumed steroids had comparable patient and graft survival rates, but a higher incidence of rejection and higher serum creatinine levels. Patients who never came off steroids had the worst outcomes. In order to identify which pediatric renal transplant recipients are most likely to benefit from steroid withdrawal, prospective, randomized trials with well-defined criteria will likely be necessary.

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